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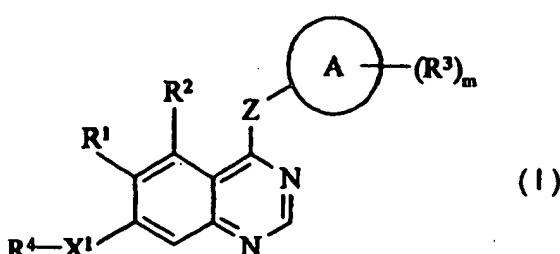
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(54) Title: QUINAZOLINE COMPOUNDS



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provided that when ring A is a 5- or 6-membered heterocyclic ring, at least one R² is either hydroxy or halogeno; X¹ is -O-, -CH₂-, -S-, -SO-, -SO₂-, -NR⁷-, -NR⁷CO-, -CONR⁷-, -SO₂NR⁷- or -NR⁷SO₂- (wherein R⁷ is hydrogen, C₁-alkyl or C₁-alkoxyC₂-alkyl); and R⁴ is selected from a number of groups defined herein comprising an C₂-alkylene, C₃-alkenylene or C₃-alkynylene chain wherein each methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno, amino and C₁-alkanoyloxy; provisos are as defined herein. The invention also relates to pharmaceutical compositions comprising a compound of formula (I), to the use of a compound of formula (I) in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal and to a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal in need of such treatment. The compounds are useful in disease states such as cancer, rheumatoid arthritis and psoriasis.

(57) Abstract: The invention concerns compounds of the formula (I) wherein ring A is phenyl or 5- or 6-membered heterocyclic ring as defined herein; Z is -O-, -NH- or -S-; m is an integer from 0 to 5 inclusive; R¹ is hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C₁-alkyl, C₁-alkoxy, C₁-alkylthio, or -NR⁵R⁶ (wherein R⁵ and R⁶, which may be the same or different, are hydrogen or C₁-alkyl); R² is hydrogen, hydroxy, halogeno, C₁-alkyl, C₁-alkoxy, trifluoromethyl, amino or nitro; R³ is hydroxy, halogeno, C₁-alkyl, C₁-alkoxy, C₁-alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

QUINAZOLINE COMPOUNDS

The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand

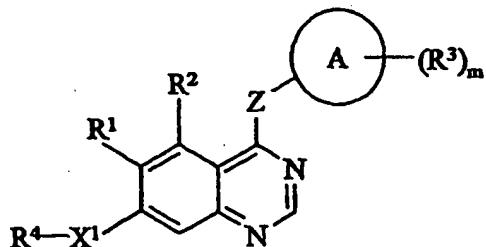
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to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by 5 amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, 10 Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

Compounds of the present invention inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular 15 permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

Compounds of the present invention possess higher potency against VEGF receptor 20 tyrosine kinase whilst possessing some activity against EGF receptor tyrosine kinase. Furthermore, compounds of the present invention, possess substantially higher potency against VEGF receptor tyrosine kinase than against EGF receptor tyrosine kinase or FGF R1 receptor tyrosine kinase.

According to the present invention there is provided a quinazoline derivative of the 25 formula I:



[wherein:

ring A is phenyl or a 5-or 6-membered heterocyclic ring which may be saturated, partially saturated or unsaturated and may be aromatic or non-aromatic and which contains 1, 2 or 3 ring heteroatoms selected from O, N and S;

5 Z is -O-, -NH- or -S-;

m is an integer from 0 to 5 inclusive;

R¹ is hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylthio, or -NR⁵R⁶ (wherein R⁵ and R⁶, which may be the same or different, are hydrogen or C₁₋₃alkyl);

10 R² is hydrogen, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, amino or nitro;

R³ is hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino or nitro; provided that when ring A is a 5- or 6-membered heterocyclic ring, at least one R³ is either hydroxy or halogeno;

X¹ is -O-, -CH₂-, -S-, -SO-, -SO₂-, -NR⁷-, -NR⁷'CO-, -CONR⁷-, -SO₂NR⁷- or -NR⁷'SO₂-;

15 (wherein R⁷ is hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

R⁴ is selected from one of the following groups:

1) -Y¹X²COR⁸ [wherein -Y¹ - is a C₂₋₅alkylene chain wherein each methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno, amino and C₁₋₄alkanoyloxy, provided that there is at least 1 and no

20 more than 3 substituents on the C₂₋₅alkylene chain; X² is -O- or -NR⁹- (in which R⁹ is hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁸ is C₁₋₃alkyl, -NR¹⁰R¹¹ or -OR¹² (wherein R¹⁰, R¹¹ and R¹², which may be the same or different, are hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)];

2) -Y² - X³R¹³ [wherein -Y² - is C₂₋₅alkylene, C₃₋₅alkenylene or C₃₋₅alkynylene wherein each

25 methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno, amino and C₁₋₄alkanoyloxy, provided that there is at least 1 substituent and no more than 3 substituents on the alkylene, alkenylene or alkynylene chain; X³ is -O-, -S-, -SO-, -SO₂-, -OCO-, -NR⁷'CO-, -CONR⁷-, -SO₂NR⁷-, -NR⁷'SO₂- or -NR⁷- (wherein R⁷ is as hereinabove defined) and R¹³ is hydrogen or C₁₋₃alkyl,

30 wherein the C₁₋₃alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy;

3) $-Y^1-X^6C_{1,5}alkylR^{14}$ [wherein Y^1 is as hereinabove defined and X^6 is $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^7CO-$, $-CONR^7-$, $-SO_2NR^7-$, $-NR^7SO_2-$ or $-NR^7-$ (wherein R^7 is as hereinabove defined) and R^{14} is $C_{3,7}$ cycloalkyl or a 3 to 7 membered saturated or partially saturated heterocyclic group containing up to 3 ring heteroatoms selected independently from O, S and N, wherein

5 the carbocyclic or heterocyclic group is optionally substituted by one or two substituents selected from oxo, hydroxy, halogeno, $C_{1,4}alkyl$, (wherein the $C_{1,4}alkyl$ group is optionally substituted by 1 or 2 substituents selected from hydroxy, cyano, halogeno, amino, nitro, morpholino, $C_{3,5}$ cycloalkyl, piperidin-1-yl and piperazin-1-yl), $C_{2,4}alkenyl$, $C_{2,4}alkynyl$, $C_{1,4}hydroxyalkyl$, $C_{1,4}alkoxy$, carbamoyl, $C_{1,3}alkylcarbamoyl$, N,N -di($C_{1,3}alkyl$)carbamoyl, C_2 alkanoyl, $C_{1,4}alkoxycarbonyl$, $C_{1,4}alkylthio$, $C_{1,4}alkylsulphanyl$, $C_{1,4}alkylsulphonyl$, C_2 alkanoylamino, $N-C_{1,3}alkyl-C_{2,4}alkanoylamino$,

$N-C_{1,3}alkylsulphamoyl$, N,N -di-[$C_{1,3}alkyl$]sulphamoyl, $C_{1,3}alkanesulphonylamino$ and $N-C_{1,3}alkyl-C_{1,3}alkanesulphonylamino$,

or R^{14} is a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group

15 containing 1 to 3 ring heteroatoms independently selected from O, N and S, and wherein the pyridone, phenyl or heterocyclic group is optionally substituted by up to 5 substituents selected from halogeno, amino, $C_{1,4}alkyl$, $C_{1,4}alkoxy$, $C_{1,4}hydroxyalkyl$, $C_{1,4}aminoalkyl$, $C_{1,4}alkylamino$, $C_{1,4}hydroxyalkoxy$, carboxy, cyano, $C_{1,4}alkylthio$, $C_{1,4}alkylsulphanyl$, $C_{1,4}alkylsulphonyl$, $N-C_{1,3}alkylsulphamoyl$, N,N -di-[$C_{1,3}alkyl$]sulphamoyl, C_1 ,

20 $C_{1,3}alkanesulphonylamino$, $N-C_{1,3}alkyl-C_{1,3}alkanesulphonylamino$, $-CONR^{10}R^{11}$ and $-NR^{10}COR^{11}$ (wherein R^{10} and R^{11} are as hereinabove defined)];

4) $-Y^1-X^4C_{1,5}alkylX^5R^{15}$ [wherein Y^1 is as hereinabove defined and X^4 and X^5 which may be the same or different are each $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^7CO-$, $-CONR^7-$, $-SO_2NR^7-$, $-NR^7SO_2-$ or $-NR^7-$ (wherein R^7 is as hereinabove defined and R^{15} is hydrogen or $C_{1,3}alkyl$)];

25 5) $-Y^1-O-C_{1,3}alkyl$ (wherein Y^1 is as hereinabove defined) provided that X^1 is $-O-$, $-S-$, $-SO-$ or $-SO_2-$;

6) $-Y^2-R^{16}$ {wherein $-Y^2-$ is as hereinabove defined and R^{16} is a saturated or partially saturated 3 to 7 membered heterocyclic ring containing up to 3 heteroatoms selected from O, S and N [wherein the heterocyclic ring is optionally substituted by up to 3 substituents selected from

30 oxo, hydroxy, halogeno, $C_{1,4}alkyl$, $C_{2,4}alkenyl$, $C_{2,4}alkynyl$ and $C_{3,7}$ cycloalkyl (wherein $C_{1,4}alkyl$, $C_{2,4}alkenyl$, $C_{2,4}alkynyl$ and $C_{3,7}$ cycloalkyl are themselves optionally substituted by up

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$_$ alkanoyloxy, trifluoromethyl, amino, nitro and R¹⁴ as hereinabove defined), C₁₋₄ alkoxy, carbamoyl, C₁₋₄ alkylcarbamoyl, N-N- di(C₁₋₄ alkyl)carbamoyl, C₂₋₄ alkanoyl, C₁₋₄ alkoxy carbonyl, C₃₋₇ cycloalkyl, C₁₋₄ alkylthio, C₁₋₄ alkylsulphanyl, C₁₋₄ alkylsulphonyl, C₂₋₄ alkanoylamino, N-C₁₋₃ alkyl-C₂₋₄ alkanoylamino, N-C₁₋₃ alkylsulphamoyl, N,N-di-[C₁₋₄ alkyl]sulphamoyl, C₁₋₃ alkanesulphonylamino and N-C₁₋₃ alkyl-C₁₋₃ alkanesulphonylamino or R¹⁶ is a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group containing 1 to 3 ring heteroatoms independently selected from O, N and S, and wherein the pyridone, phenyl or heterocyclic group is optionally substituted by up to 5 substituents selected from halogeno, amino, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ hydroxyalkyl, C₁₋₄ aminoalkyl, C₁₋₄ alkylamino, C₁₋₄ hydroxyalkoxy, carboxy, cyano, C₁₋₄ alkylthio, C₁₋₄ alkylsulphanyl, C₁₋₄ alkylsulphonyl, N-C₁₋₃ alkylsulphamoyl, N,N-di-[C₁₋₃ alkyl]sulphamoyl, C₁₋₃ alkanesulphonylamino, N-C₁₋₃ alkyl-C₁₋₃ alkanesulphonylamino, -CONR¹⁰R¹¹ and -NR¹⁰COR¹¹ (wherein R¹⁰ and R¹¹ are as hereinabove defined)];

7) -Y²-X⁶-R¹⁴ (wherein Y², X⁶ and R¹⁴ are as hereinabove defined); and

15 8) -Y²-NR¹⁷R¹⁸ [wherein Y² is as hereinabove defined and R¹⁷ and R¹⁸ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl or C₁₋₃ alkoxyC₁₋₆ alkyl (wherein any alkyl group in R¹⁷ or R¹⁸ is optionally substituted by up to 2 substituents selected from hydroxy, halogeno, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkanoyloxy, trifluoromethyl, cyano, amino or nitro)];

20 9) -Y³-R^a (wherein Y³ is C₁₋₅ alkylene, C₂₋₅ alkenylene or C₂₋₅ alkynylene wherein each methylene group (other than that of the α -carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno, amino and C₁₋₄ alkanoyloxy, provided that there are no more than 3 substituents on the alkylene, alkenylene or alkynylene chain; and R^a is C₃₋₇ cycloalkyl which is substituted by 1 substituent selected from hydroxy, amino and halogeno on the ring carbon linked to Y³ and additionally optionally substituted by up to 3 substituents selected from oxo, hydroxy, halogeno, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, carbamoyl, C₁₋₄ alkylcarbamoyl, N-N- di(C₁₋₄ alkyl)carbamoyl, C₂₋₄ alkanoyl, C₁₋₄ alkoxy carbonyl and C₃₋₇ cycloalkyl (wherein C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl and C₃₋₇ cycloalkyl are themselves optionally substituted by up to 3 substituents selected from hydroxy, halogeno, cyano, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkanoyloxy, trifluoromethyl, cyano, amino, nitro and R¹⁴ as hereinabove defined)];

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provided that when:

m is an integer from 1 to 3;

R¹ is methoxy; R² is hydrogen; Z is -NH-;

R³ is halogeno or C₁₋₃alkyl; and

5 X¹ is -O-; then

R⁴ is not selected from one of the following three groups:

a) -C₂₋₅alkylR¹⁹ (wherein R¹⁹ is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

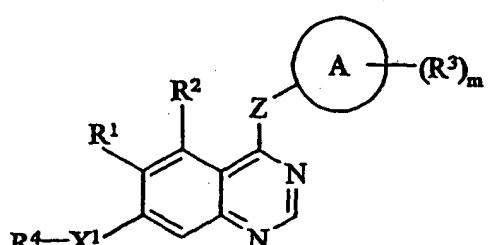
b) -C₂₋₅alkenylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

10 c) -C₂₋₅alkynylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

wherein any alkylene, alkenylene or alkynylene chain in groups a) to c) above are optionally substituted by one or more substituents selected from hydroxy, halogeno and amino; or a pharmaceutically-acceptable salt or prodrug thereof.

According to another aspect of the present invention there is provided a quinazoline

15 derivative of the formula I:



(I)

[wherein:

ring A is phenyl or a 5-or 6-membered heterocyclic ring which may be saturated, partially

20 saturated or unsaturated and may be aromatic or non-aromatic and which contains 1, 2 or 3 ring heteroatoms selected from O, N and S;

Z is -O-, -NH- or -S-;

m is an integer from 0 to 5 inclusive;

R¹ is hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C₁₋₃alkyl,

25 C₁₋₃alkoxy, C₁₋₃alkylthio, or -NR⁵R⁶ (wherein R⁵ and R⁶, which may be the same or different, are hydrogen or C₁₋₃alkyl);

R² is hydrogen, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, amino or nitro;

R^3 is hydroxy, halogeno, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkanoyloxy, trifluoromethyl, cyano, amino or nitro; provided that when ring A is a 5- or 6-membered heterocyclic ring, at least one R^3 is either hydroxy or halogeno;

X^1 is -O-, - CH_2 -, -S-, -SO-, - SO_2 -, -NR⁷-, -NR⁷'CO-, -CONR⁷-, - SO_2 NR⁷- or -NR⁷'SO₂-,

5 (wherein R^7 is hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl);

R^4 is selected from one of the following groups:

1) -Y¹X²COR⁸ [wherein -Y¹ - is a C_{2-5} alkylene chain wherein each methylene group (other than that of the α -carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno and amino, provided that there is at least 1 and no more than 3

10 substituents on the C_{2-5} alkylene chain; X² is -O- or -NR⁹- (in which R⁹ is hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl) and R⁸ is C_{1-3} alkyl, -NR¹⁰R¹¹ or -OR¹² (wherein R¹⁰, R¹¹ and R¹², which may be the same or different, are hydrogen, C_{1-3} alkyl or C_{1-3} alkoxyC₂₋₃alkyl)];

2) -Y²-X³R¹³ [wherein -Y²- is C_{2-5} alkylene, C_{3-5} alkenylene or C_{3-5} alkynylene wherein each methylene group (other than that of the α -carbon) is optionally substituted by 1 substituent

15 independently selected from hydroxy, halogeno and amino, provided that there is at least 1 substituent and no more than 3 substituents on the alkylene, alkenylene or alkynylene chain; X³ is -O-, -S-, -SO-, - SO_2 -, -OCO-, -NR⁷'CO-, -CONR⁷-, - SO_2 NR⁷-, -NR⁷'SO₂- or -NR⁷- (wherein R⁷ is as hereinabove defined) and R¹³ is hydrogen or C_{1-3} alkyl, wherein the C_{1-3} alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C_{1-4} alkoxy;

20 3) -Y¹-X⁶C₁₋₅alkylR¹⁴ [wherein Y¹ is as hereinabove defined and X⁶ is -O-, -S-, -SO-, - SO_2 -, -NR⁷'CO-, -CONR⁷-, - SO_2 NR⁷-, -NR⁷'SO₂- or -NR⁷- (wherein R⁷ is as hereinabove defined) and R¹⁴ is C_{3-7} cycloalkyl or a 3 to 7 membered saturated or partially saturated heterocyclic group containing up to 3 ring heteroatoms selected independently from O, S and N, wherein the carbocyclic or heterocyclic group is optionally substituted by one or two substituents

25 selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, (wherein the C_{1-4} alkyl group is optionally substituted by 1 or 2 substituents selected from hydroxy, cyano, halogeno, amino, nitro, morpholino, C_{3-5} cycloalkyl, piperidin-1-yl and piperazin-1-yl), C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, carbamoyl, C_{1-3} alkylcarbamoyl, N,N-di(C_{1-3} alkyl)carbamoyl, C_{2-4} alkanoyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylthio, C_{1-4} alkylsulphinyl, C_{1-4} alkylsulphonyl, C_{2-4}

30 alkanoylamino, N- C_{1-3} alkyl-C₂₋₄alkanoylamino,

N- C_{1-3} alkylsulphamoyl, N,N-di-[C_{1-3} alkyl]sulphamoyl, C_{1-3} alkanesulphonylamino and

N-C₁₋₃alkyl- C₁₋₃alkanesulphonylamino,
 or R¹⁴ is a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group containing 1 to 3 ring heteroatoms independently selected from O, N and S, and wherein the pyridone, phenyl or heterocyclic group is optionally substituted by up to 5 substituents

5 selected from halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, C₁₋₄alkylthio, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, N-C₁₋₃alkylsulphamoyl, N,N-di-[C₁₋₃alkyl]sulphamoyl, C₁₋₃alkanesulphonylamino, N-C₁₋₃alkyl-C₁₋₃alkanesulphonylamino, -CONR¹⁰R¹¹ and -NR¹⁰COR¹¹ (wherein R¹⁰ and R¹¹ are as hereinabove defined)];

10 4) -Y¹-X⁴C₁₋₃alkylX⁵R¹⁵ [wherein Y¹ is as hereinabove defined and X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR⁷CO-, -CONR⁷-, -SO₂NR⁷-, -NR⁷SO₂- or -NR⁷- (wherein R⁷ is as hereinabove defined and R¹⁵ is hydrogen or C₁₋₃alkyl)];
 5) -Y¹-O-C₁₋₃alkyl (wherein Y¹ is as hereinabove defined) provided that X¹ is -O-, -S-, -SO- or -SO₂;

15 6) -Y²-R¹⁶ {wherein -Y²- is as hereinabove defined and R¹⁶ is a saturated or partially saturated 3 to 7 membered heterocyclic ring containing up to 3 heteroatoms selected from O, S and N [wherein the heterocyclic ring is optionally substituted by up to 3 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl and C₃₋₇cycloalkyl (wherein C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl and C₃₋₇cycloalkyl are themselves optionally substituted by up

20 to 3 substituents selected from hydroxy, halogeno, cyano, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, amino, nitro and R¹⁴ as hereinabove defined), C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₂₋₄alkanoyl, C₁₋₄alkoxycarbonyl, C₃₋₇cycloalkyl, C₁₋₄alkylthio, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₂₋₄alkanoylamino, N-C₁₋₃alkyl-C₂₋₄alkanoylamino, N-C₁₋₃alkylsulphamoyl, N,N-di-[C₁₋₃alkyl]sulphamoyl, C₁₋₃alkanesulphonylamino and N-C₁₋₃alkyl- C₁₋₃alkanesulphonylamino

25 or R¹⁶ is a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group containing 1 to 3 ring heteroatoms independently selected from O, N and S, and wherein the pyridone, phenyl or heterocyclic group is optionally substituted by up to 5 substituents selected from halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, C₁₋₄alkylthio, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, N-C₁₋₃alkylsulphamoyl, N,N-di-[C₁₋₃alkyl]sulphamoyl, C₁₋₃alkanesulphonylamino, N-C₁₋₃alkyl-C₁₋₃alkanesulphonylamino, -CONR¹⁰R¹¹ and -NR¹⁰COR¹¹ (wherein R¹⁰ and R¹¹ are as hereinabove defined)];

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$_$ alkanesulphonylamino, \underline{N} - C_{1_3} alkyl- C_{1_3} alkanesulphonylamino, -CONR¹⁰R¹¹ and -NR¹⁰COR¹¹ (wherein R¹⁰ and R¹¹ are as hereinabove defined)];

7) -Y²-X⁶-R¹⁴ (wherein Y², X⁶ and R¹⁴ are as hereinabove defined); and

8) -Y²-NR¹⁷R¹⁸ [wherein Y² is as hereinabove defined and R¹⁷ and R¹⁸ are independently selected from hydrogen, C_{1_6}alkyl, C_{2_6}alkenyl, C_{2_6}alkynyl or C_{1_3}alkoxyC_{1_6}alkyl (wherein any alkyl group in R¹⁷ or R¹⁸ is optionally substituted by up to 2 substituents selected from hydroxy, halogeno, C_{1_3}alkyl, C_{1_3}alkoxy, C_{1_3}alkanoyloxy, trifluoromethyl, cyano, amino or nitro)];

9) -Y³-R^a (wherein Y³ is C_{1_5}alkylene, C_{2_5}alkenylene or C_{2_5}alkynylene wherein each methylene group (other than that of the α -carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno and amino, provided that there are no more than 3 substituents on the alkylene, alkenylene or alkynylene chain; and R^a is C_{3_7}cycloalkyl which is substituted by 1 substituent selected from hydroxy, amino and halogeno on the ring carbon linked to Y³ and additionally optionally substituted by up to 3 substituents selected from oxo, hydroxy, halogeno, C_{1_4}alkyl, C_{2_4}alkenyl, C_{2_4}alkynyl, C_{1_4}alkoxy, carbamoyl, C_{1_4}alkylcarbamoyl, \underline{N} - N -di(C_{1_4}alkyl)carbamoyl, C_{2_4}alkanoyl, C_{1_4}alkoxycarbonyl and C_{3_7}cycloalkyl (wherein C_{1_4}alkyl, C_{2_4}alkenyl, C_{2_4}alkynyl and C_{3_7}cycloalkyl are themselves optionally substituted by up to 3 substituents selected from hydroxy, halogeno, cyano, C_{1_3}alkyl, C_{1_3}alkoxy, C_{1_3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and R¹⁴ as hereinabove defined)];

provided that when:

m is an integer from 1 to 3;

R¹ is methoxy; R² is hydrogen; Z is -NH-;

R³ is halogeno or C_{1_3}alkyl; and

25 X¹ is -O-; then

R⁴ is not selected from one of the following three groups:

a) -C_{2_5}alkylR¹⁹ (wherein R¹⁹ is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, C_{1_4}alkyl, C_{1_4}hydroxyalkyl and C_{1_4}alkoxy);

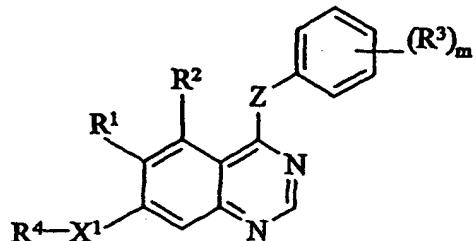
b) -C_{2_5}alkenylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

30 c) -C_{2_5}alkynylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

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or a pharmaceutically-acceptable salt or prodrug thereof.

According to another aspect of the present invention there is provided a quinazoline derivative of the formula I:



5

(I)

[wherein:

Z is -O-, -NH- or -S-;

m is an integer from 0 to 5 inclusive;

R¹ is hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C₁₋₃alkyl,

10 C₁₋₃alkoxy, C₁₋₃alkylthio, or -NR⁵R⁶ (wherein R⁵ and R⁶, which may be the same or different, are hydrogen or C₁₋₃alkyl);

R² is hydrogen, hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, amino or nitro;

R³ is hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino or nitro;

15 X¹ is -O-, -CH₂-, -S-, -SO-, -SO₂-, -NR⁷-, -NR⁷CO-, -CONR⁷-, -SO₂NR⁷- or -NR⁷SO₂-, (wherein R⁷ is hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl);

R⁴ is selected from one of the following groups:

1) -Y¹X²COR⁸ [wherein -Y¹ - is a C₂₋₅alkylene chain wherein each methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected

20 from hydroxy, halogeno and amino, provided that there is at least 1 and no more than 3 substituents on the C₂₋₅alkylene chain; X² is -O- or -NR⁹ - (in which R⁹ is hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁸ is C₁₋₃alkyl, -NR¹⁰R¹¹ or -OR¹² (wherein R¹⁰, R¹¹ and

R¹², which may be the same or different, are hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)];

2) -Y²- X³R¹³ [wherein -Y² - is C₂₋₅alkylene, C₃₋₅alkenylene or C₃₋₅alkynylene wherein each

25 methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno and amino, provided that there is at least 1 substituent and no more than 3 substituents on the alkylene, alkenylene or alkynylene chain;

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X^3 is -O-, -S-, -SO-, -SO₂-, -OCO-, -NR⁷CO-, -CONR⁷-, -SO₂NR⁷-, -NR⁷SO₂- or -NR⁷- (wherein R⁷ is as hereinabove defined) and R¹³ is hydrogen or C₁₋₃alkyl, wherein the C₁₋₃alkyl group may bear one or two substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy; 3) -Y¹-X⁶C₁₋₃alkylR¹⁴ [wherein Y¹ is as hereinabove defined and X⁶ is -O-, -S-, -SO-, -SO₂-, -

5 NR⁷CO-, -CONR⁷-, -SO₂NR⁷-, -NR⁷SO₂- or -NR⁷- (wherein R⁷ is as hereinabove defined) and R¹⁴ is C₃₋₇ cycloalkyl or a 3 to 7 membered saturated or partially saturated heterocyclic group containing up to 3 ring heteroatoms selected independently from O, S and N, wherein the carbocyclic or heterocyclic group is optionally substituted by one or two substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, (wherein the C₁₋₄alkyl group is optionally

10 substituted by 1 or 2 substituents selected from hydroxy, cyano, halogeno, amino, nitro, morpholino, C₃₋₅cycloalkyl, piperidin-1-yl and piperazin-1-yl), C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, carbamoyl, C₁₋₃alkylcarbamoyl, N,N-di(C₁₋₃alkyl)carbamoyl, C₂₋₄alkanoyl, C₁₋₄alkoxycarbonyl, C₁₋₄alkylthio, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₂₋₄alkanoylamino, N-C₁₋₃alkyl-C₂₋₄alkanoylamino, N-C₁₋₃alkylsulphamoyl, N,N-di-[C₁₋₃alkyl]sulphamoyl, C₁₋₃alkanesulphonylamino and N-C₁₋₃alkyl- C₁₋₃alkanesulphonylamino,

15 or R¹⁴ is a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group containing 1 to 3 ring heteroatoms independently selected from O, N and S, and wherein the pyridone, phenyl or heterocyclic group is optionally substituted by up to 5 substituents selected from halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, C₁₋₄alkylthio, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, N-C₁₋₃alkylsulphamoyl, N,N-di-[C₁₋₃alkyl]sulphamoyl, C₁₋₃alkanesulphonylamino, N-C₁₋₃alkyl-C₁₋₃alkanesulphonylamino, -CONR¹⁰R¹¹ and -NR¹⁰COR¹¹ (wherein R¹⁰ and R¹¹ are as hereinabove defined)];

4) -Y¹-X⁴C₁₋₃alkylX⁵R¹⁵ [wherein Y¹ is as hereinabove defined and X⁴ and X⁵ which may be

25 the same or different are each -O-, -S-, -SO-, -SO₂-, -NR⁷CO-, -CONR⁷-, -SO₂NR⁷-, -NR⁷SO₂- or -NR⁷- (wherein R⁷, is as hereinabove defined and R¹⁵ is hydrogen or C₁₋₃alkyl)];

5) -Y¹-O- C₁₋₃alkyl (wherein Y¹ is as hereinabove defined) provided that X¹ is -O-, -S-, -SO- or -SO₂;

6) -Y²-R¹⁶ {wherein -Y²- is as hereinabove defined and R¹⁶ is a saturated or partially saturated

30 3 to 7 membered heterocyclic ring containing up to 3 heteroatoms selected from O, S and N [wherein the heterocyclic ring is optionally substituted by up to 3 substituents selected from

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$\text{C}_1\text{-alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$ and $\text{C}_{3-7}\text{cycloalkyl}$ are themselves optionally substituted by up to 3 substitutents selected from hydroxy, halogeno, cyano, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, $\text{C}_{1-3}\text{alkanoyloxy}$, trifluoromethyl, amino, nitro and R^{14} as hereinabove defined), $\text{C}_{1-4}\text{alkoxy}$, carbamoyl, $\text{C}_{1-4}\text{alkylcarbamoyl}$, $\text{N-N-di}(\text{C}_{1-4}\text{alkyl})\text{carbamoyl}$, $\text{C}_{2-4}\text{alkanoyl}$, C_{1-3}

5 alkoxycarbonyl , $\text{C}_{3-7}\text{cycloalkyl}$, $\text{C}_{1-4}\text{alkylthio}$, $\text{C}_{1-4}\text{alkylsulphinyl}$, $\text{C}_{1-4}\text{alkylsulphonyl}$, $\text{C}_{2-4}\text{alkanoylamino}$, $\text{N-C}_{1-3}\text{alkyl-C}_{2-4}\text{alkanoylamino}$, $\text{N-C}_{1-3}\text{alkylsulphamoyl}$, $\text{N,N-di-[C}_{1-3}\text{alkyl]sulphamoyl}$, $\text{C}_{1-3}\text{alkanesulphonylamino}$ and $\text{N-C}_{1-3}\text{alkyl-C}_{1-3}\text{alkanesulphonylamino}$ or R^{16} is a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group containing 1 to 3 ring heteroatoms independently selected from O, N and S, and wherein the

10 pyridone, phenyl or heterocyclic group is optionally substituted by up to 5 substituents selected from halogeno, amino, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$, $\text{C}_{1-4}\text{hydroxyalkyl}$, $\text{C}_{1-4}\text{aminoalkyl}$, $\text{C}_{1-4}\text{alkylamino}$, $\text{C}_{1-4}\text{hydroxyalkoxy}$, carboxy, cyano, $\text{C}_{1-4}\text{alkylthio}$, $\text{C}_{1-4}\text{alkylsulphinyl}$, $\text{C}_{1-4}\text{alkylsulphonyl}$, $\text{N-C}_{1-3}\text{alkylsulphamoyl}$, $\text{N,N-di-[C}_{1-3}\text{alkyl]sulphamoyl}$, $\text{C}_{1-3}\text{alkanesulphonylamino}$, $\text{N-C}_{1-3}\text{alkyl-C}_{1-3}\text{alkanesulphonylamino}$, $-\text{CONR}^{10}\text{R}^{11}$ and $-\text{NR}^{10}\text{COR}^{11}$

15 (wherein R^{10} and R^{11} are as hereinabove defined)];

7) $-\text{Y}^2\text{-X}^6\text{-R}^{14}$ (wherein Y^2 , X^6 and R^{14} are as hereinabove defined); and

8) $-\text{Y}^2\text{-NR}^{17}\text{R}^{18}$ [wherein Y^2 is as hereinabove defined and R^{17} and R^{18} are independently selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$ or $\text{C}_{1-3}\text{alkoxyC}_{1-6}\text{alkyl}$ (wherein any alkyl group in R^{17} or R^{18} is optionally substituted by up to 2 substituents selected from

20 hydroxy, halogeno, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, $\text{C}_{1-3}\text{alkanoyloxy}$, trifluoromethyl, cyano, amino or nitro)];

9) $-\text{Y}^3\text{-R}^a$ (wherein Y^3 is $\text{C}_{1-3}\text{alkylene}$, $\text{C}_{2-5}\text{alkenylene}$ or $\text{C}_{2-5}\text{alkynylene}$ wherein each methylene group (other than that of the α -carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno and amino, provided that there are no more

25 than 3 substituents on the alkylene, alkenylene or alkynylene chain; and R^a is $\text{C}_{3-7}\text{cycloalkyl}$ which is substituted by 1 substituent selected from hydroxy, amino and halogeno on the ring carbon linked to Y^3 and additionally optionally substituted by up to 3 substituents selected from oxo, hydroxy, halogeno, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$, $\text{C}_{1-4}\text{alkoxy}$, carbamoyl, $\text{C}_{1-4}\text{alkylcarbamoyl}$, $\text{N-N-di}(\text{C}_{1-4}\text{alkyl})\text{carbamoyl}$, $\text{C}_{2-4}\text{alkanoyl}$, $\text{C}_{1-4}\text{alkoxycarbonyl}$ and $\text{C}_{3-7}\text{cycloalkyl}$ (wherein $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$ and $\text{C}_{3-7}\text{cycloalkyl}$ are themselves optionally substituted by up to 3 substituents selected from hydroxy, halogeno, cyano, C_{1-4}

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,alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro and R¹⁴ as hereinabove defined);

provided that when:

m is an integer from 1 to 3;

5 R¹ is methoxy; R² is hydrogen; Z is -NH-;

R³ is halogeno or C₁₋₃alkyl; and

X¹ is -O-; then

R⁴ is not selected from one of the following three groups:

a) -C₂₋₅alkylR¹⁹ (wherein R¹⁹ is piperidin-4-yl which may bear one or two substituents

10 selected from hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

b) -C₂₋₅alkenylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

c) -C₂₋₅alkynylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

wherein any alkylene, alkenylene or alkynylene chain in groups a) to c) above are optionally substituted by one or more substituents selected from hydroxy, halogeno and amino;

15 or a pharmaceutically-acceptable salt or prodrug thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An

20 analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms

25 may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

In formula I, as hereinbefore defined, hydrogen will be present at positions 2 and 8 of
30 the quinazoline group.

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drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

5 It is also to be understood that certain quinazolines of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when X¹ is, for example,
10 a group of formula -NR⁷CO-, it is the nitrogen atom bearing the R⁷ group which is attached to the quinazoline ring and the carbonyl (CO) group is attached to R⁴, whereas when X¹ is, for example, a group of formula -CONR⁷-, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom bearing the R⁷ group is attached to R⁴. A similar convention applies to the other two atom X¹ linking groups. When X¹ is -NR⁷- it is the
15 nitrogen atom bearing the R⁷ group which is linked to the quinazoline ring and to R⁴. An analogous convention applies to other groups. It is further to be understood that when X¹ is -NR⁷- and R⁷ is C_{1,3}alkoxyC_{2,3}alkyl it is the C_{2,3}alkyl moiety which is linked to the nitrogen atom of X¹ and an analogous convention applies to other groups.

The α-carbon in the alkylene, alkenylene or alkynylene chains in Y¹ and Y² is the
20 carbon atom in the chain which is linked to X¹. The β-carbon is the carbon atom in the carbon chain linked to the α-carbon.

Preferred values for Y¹ include 2-acetoxypropylene, 2-hydroxyethylene, 2-hydroxypropylene, 3-hydroxypropylene, 2-hydroxybutylene, 3-hydroxybutylene and 4-hydroxybutylene.

25 Suitable values for Y¹ include 2-hydroxyethylene, 2-hydroxypropylene, 3-hydroxypropylene, 2-hydroxybutylene, 3-hydroxybutylene and 4-hydroxybutylene.

Suitable values for Y² include those mentioned above for Y¹ and 2-hydroxybut-3-enylene, 2-hydroxypent-3-enylene, 4-hydroxybut-2-enylene and 3-hydroxypent-4-enylene.

More preferred values of Y¹ are 2-hydroxypropylene and 2-acetoxypropylene.

30 More preferred values of Y² are 2-hydroxypropylene and 2-acetoxypropylene.

morpholine, thiomorpholine, (tetrahydro-1,4-thiazine), thiazolidine, 1,2,6-tetrahydropyridine, tetrahydrofuran, tetrahydropyran, 1,1-dioxotetrahydro-1,4-thiazine, homopiperazine dihydropyridine, tetrahydropyridine, dihydropyrimidine and tetrahydropyrimidine.

Examples of 5 or 6 membered aromatic heterocyclic groups for ring A include furan,
 5 pyrrole, thiophene, oxazole, isoxazole, imidazole, pyrazole, thiazole, isothiazole, oxadiazole, thiadiazole, triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,3,5-triazine, indole.

Examples of suitable 3 to 7 membered saturated or partially saturated heterocyclic groups for R¹⁴ and R¹⁶ include pyrrolidine, piperidine, aziridine, azetidine, piperazine,
 10 homopiperidine, pyrrolidine, morpholine, thiomorpholine, (tetrahydro-1,4-thiazine), thiazolidine, 1,2,6-tetrahydropyridine, tetrahydrofuran, tetrahydropyran, 1,1-dioxotetrahydro-1,4-thiazine, homopiperazine dihydropyridine, tetrahydropyridine, dihydropyrimidine and tetrahydropyrimidine.

Examples of suitable C₃₋₇cycloalkyl groups in R¹⁴, R¹⁶ and R^a include, cyclopropyl,
 15 cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Particularly cyclopropyl, cyclopentyl and cyclohexyl.

Examples of 5 or 6 membered aromatic heterocyclic groups for R¹⁴ and R¹⁶ include furan, pyrrole, thiophene, oxazole, isoxazole, imidazole, pyrazole, thiazole, isothiazole, oxadiazole, thiadiazole, triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,3,5-20 triazine, indole.

Preferred 5 or 6-membered aromatic heterocyclic groups for R¹⁴ and R¹⁶ include pyridine, imidazole, thiophene, triazole, and pyridazine. Most preferably pyridine, imidazole or triazole.

Suitable values for any of the 'R' groups (R¹ to R¹⁹), or for various substituent groups
 25 on an alkyl chain or ring system in R⁴ include:-

for halogeno	fluoro, chloro, bromo and iodo;
for C ₁₋₆ alkyl:	methyl, ethyl, propyl, isopropyl and <u>tert</u> -butyl;
for C ₂₋₃ alkenyl:	vinyl, allyl and but-2-enyl;
30 for C ₂₋₃ alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for C ₁₋₆ alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;

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for C₂₋₆alkenyloxy: vinyloxy and allyloxy;

for C₂₋₆alkynyoxy: ethynyloxy and 2-propynyoxy;

for C₁₋₄alkylthio: methylthio, ethylthio and propylthio;

for C₁₋₄alkylsulphinyl: methylsulphinyl and ethylsulphinyl;

5 for C₁₋₄alkylsulphonyl: methylsulphonyl and ethylsulphonyl;

for C₁₋₄alkylamino: methylamino, ethylamino, propylamino, isopropylamino and butylamino;

for di-[C₁₋₄alkyl]amino: dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;

10 for C₁₋₄alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;

for N-C₁₋₄alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

for N,N-di-[C₁₋₄alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;

15 for C₂₋₄alkanoyl: acetyl and propionyl;

for C₁₋₄alkanoyloxy: acetoxy and propionyloxy;

for C₂₋₄alkanoylamino: acetamido and propionamido;

for N-C₁₋₃alkyl-C₂₋₄alkanoylamino: N-methylacetamido and N-methylpropionamido;

20 for N-C₁₋₃alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;

for N,N-di-[C₁₋₃alkyl]sulphamoyl: N,N-dimethylsulphamoyl;

for C₁₋₃alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;

for N-C₁₋₃alkyl-C₁₋₃alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino.

25 Preferred substituents for saturated or partially saturated heterocyclic groups in R¹⁴ and R¹⁶ include oxo, hydroxy, halogeno, C₁₋₄alkyl, (wherein the C₁₋₄alkyl group is optionally substituted by 1 or 2 substituents selected from hydroxy, cyano, halogeno, amino, nitro, morpholino, C₃₋₅cycloalkyl, piperidin-1-yl and piperazin-1-yl), C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, carbamoyl, C₁₋₃alkylcarbamoyl, N,N-di(C₁₋₃alkyl)carbamoyl, C₂₋₄alkanoyl and C₁₋₄alkoxycarbonyl.

$\text{C}_{1-4}\text{alkyl}$, (wherein the $\text{C}_{1-4}\text{alkyl}$ group is optionally substituted by 1 or 2 substituents selected from hydroxy, cyano, halogeno, amino, morpholino, $\text{C}_{3-5}\text{cycloalkyl}$, piperidin-1-yl and piperazin-1-yl), $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$, $\text{C}_{1-4}\text{alkoxy}$, carbamoyl, $\text{C}_{1-3}\text{alkylcarbamoyl}$, N,N-di($\text{C}_{1-3}\text{alkyl}$)carbamoyl, $\text{C}_{2-4}\text{alkanoyl}$ and $\text{C}_{1-4}\text{alkoxycarbonyl}$.

5 More preferred substituents for saturated or partially saturated heterocyclic groups in R^{14} and R^{16} include oxo, hydroxy, halogeno, $\text{C}_{1-4}\text{alkyl}$ (optionally substituted by hydroxy, cyano, morpholino, cyclopentyl, piperidin-1-yl or piperazin-1-yl), allyl, $\text{C}_{1-4}\text{alkoxy}$, $\text{C}_{2-4}\text{alkanoyl}$ or $\text{C}_{1-4}\text{alkoxycarbonyl}$.

More preferred substituents for saturated or partially saturated heterocyclic groups in 10 in R^{14} and R^{16} include oxo, hydroxy, fluoro, chloro, bromo, methyl, ethyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-morpholinoethyl, cyclopropyl, allyl, methoxy, acetyl and methoxycarbonyl.

Preferred substituents for ring carbon atoms in saturated or partially saturated heterocyclic groups in R^{14} and R^{16} include hydroxy, bromo and methyl. Most preferably ring 15 carbon atoms in saturated or partially saturated heterocyclic groups in R^{14} and R^{16} are unsubstituted.

Preferred substituents for ring NH groups in saturated or partially saturated heterocyclic groups in R^{14} and R^{16} include $\text{C}_{1-4}\text{alkyl}$ (optionally substituted as hereinabove defined), $\text{C}_{2-5}\text{alkyl}$, $\text{C}_{2-4}\text{alkanoyl}$ or $\text{C}_{1-4}\text{alkoxycarbonyl}$. More preferably, $\text{C}_{1-4}\text{alkyl}$ 20 (optionally substituted by hydroxy, fluoro, chloro, bromo, cyclopentyl, morpholino, piperazin-1-yl or piperidin-1-yl), acetyl, allyl or methoxycarbonyl.

Preferably the aromatic group in R^{14} and R^{16} is substituted by up to 3 substituents. More preferably up to 2 substituents.

Preferred substituents for aromatic groups in R^{14} and R^{16} include halogeno, $\text{C}_{1-4}\text{alkyl}$, 25 amino, $\text{C}_{1-4}\text{alkoxy}$, hydroxy $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{1-4}\text{hyrdoxyalkoxy}$. More preferred substituents include fluoro, chloro, bromo, methyl, ethyl, methoxy, hydroxymethyl and 2-hydroxyethyl.

Preferably ring A is phenyl or a 5-6-membered heteroaromatic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

More preferably ring A is phenyl or a 6-membered heteroaromatic moiety which 30 contains 1-3 heteroatoms selected independently from O, N and S.

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Yet more preferably ring A is phenyl or pyridyl.

Most preferably ring A is phenyl.

In another aspect ring A is pyridyl.

Preferably m is an integer from 1 to 5 inclusive. More preferably m is 2 or 3. Most 5 preferably m is 2.

Preferably R¹ is hydrogen, hydroxy, cyano, nitro, trifluoromethyl, C_{1,3}alkyl, C₁, alkoxy or amino.

More preferably, R¹ is hydrogen, hydroxy, cyano, nitro, trifluoromethyl, methyl, ethyl, methoxy or ethoxy. Even more preferably R¹ is hydrogen, methyl or methoxy. Most 10 preferably R¹ is hydrogen or methoxy, but especially methoxy.

Preferably, R² is hydrogen, fluoro, amino or nitro. Most preferably R² is hydrogen.

Preferably R³ is hydroxy, halogeno, C_{1,2}alkyl, C_{1,2}alkoxy, trifluoromethyl, cyano, amino or nitro.

More preferably, R³ is fluoro, chloro, bromo, methyl or methoxy.

15 Particular values for ring A bearing (R³)_m are 2-fluoro-4-chloro-5-hydroxyphenyl, 2-fluoro-4-bromo-5-hydroxyphenyl, 2-fluoro-4-chlorophenyl or 2-fluoro-4-bromophenyl.

Preferably, when ring A is phenyl, m is 2 and the phenyl ring is substituted in the 2-and 4-positions.

Preferably, when ring A is phenyl, m is 2 and the phenyl ring is substituted in the 2-and 4-positions by substituents independently selected from fluoro, chloro and bromo.

More preferably, ring A bearing (R³)_m is 2-fluoro-4-chlorophenyl or 2-fluoro-4-bromophenyl. In another aspect ring A bearing (R³)_m is 2-chloro-3-methoxyphenyl, 2-bromo-3-chlorophenyl, 2,3-dibromophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2-bromo-4-chlorophenyl, 2-chloro-3-methylphenyl, 2-bromo-4-methylphenyl, 2-chloro-3-methoxyphenyl or 3-chloro-4-fluorophenyl.

Preferably X¹ is -O-, -S-, -NR⁷CO-, -NR⁷SO₂- or -NR⁷- (wherein R⁷ is hydrogen, C_{1,2}alkyl or C_{1,2}alkoxyethyl).

Preferably X¹ is -O-, -S-, -NR⁷CO- or -NR⁷SO₂- (wherein R⁷ is hydrogen, methyl or ethyl).

More preferably X¹ is -O-, -S-, -NR⁷CO- (wherein R⁷ is hydrogen or methyl).

30 Yet more preferably X¹ is -O-, or -NHCO-, or -S-. Yet more preferably X¹ is -O-, or -S-.

Most preferably X¹ is -O-.

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Preferably X^2 is -O- or -NR⁹- (wherein R⁹ is hydrogen, C₁₋₃alkyl or C₁₋₂alkoxyethyl).

Preferably X^3 is -O-, -S-, -SO-, -SO₂-, -NR⁷CO-, -NR⁷SO₂- or -NR⁷- (wherein R⁷ is hydrogen, C₁₋₂alkyl or C₁₋₂alkoxyethyl).

More preferably X^3 is -O-, -S-, -SO-, -SO₂- or -NR⁷- (wherein R⁷ is hydrogen, C₁₋₅alkyl or C₁₋₂alkoxyethyl).

Yet more preferably X^3 is -O- or -NR⁷- (wherein R⁷ is hydrogen, methyl or ethyl).

Preferably X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO₂- or -NR⁷- (wherein R⁷ is hydrogen, C₁₋₃alkyl or C₁₋₂alkoxyethyl).

More preferably X^4 and X^5 , which may be the same or different, are each -O-, -S- or -NR⁷- (wherein R⁷ is hydrogen, methyl, ethyl or C₁₋₂alkoxyethyl).

More preferably X^4 and X^5 which may be the same or different are each -O- or -NH-.

Preferably X^6 is -O-.

Preferably R⁴ is selected from one of the following groups:

- 1a) -Y¹ - X² COR⁸ (wherein Y¹, X² and R⁸ are as hereinabove defined);
- 15 2a) -Y¹ - X³ R¹³ (wherein Y¹, X² and R¹³ are as hereinabove defined);
- 3a) -Y¹ - R²⁰ (wherein Y¹ is as hereinabove defined and R²⁰ is a 3 to 7 membered saturated or partially saturated heterocyclic group containing 1 or 2 ring atoms independently selected from O, S and N wherein the heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl (optionally substituted by hydroxy, halogeno,
- 20 cyano, C₅₋₇cycloalkyl or a 5 or 6 membered saturated heterocyclic group containing one or two ring heteroatoms independently selected from O, S and N), C₂₋₅alkenyl, C₂₋₅alkynyl, C₁₋₄alkoxy, carbamoyl, C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, C₁₋₄ alkanoyl and C₁₋₄alkoxycarbonyl;
- 4a) -Y¹ - X⁴C₁₋₃alkylX⁵R¹⁵ (wherein Y¹, X⁴, X⁵ and R¹⁵ are as hereinabove defined);
- 25 5a) C₁₋₃alkoxy-Y¹-, (wherein Y¹ is as hereinabove defined) provided that X¹ is -O-, -S-, -SO- or -SO₂-;
- 6a) -Y¹ - X⁶C₁₋₃alkylR²¹ (wherein Y¹ and X⁶ are as hereinabove defined and R²¹ is cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group containing 1 or 2 ring heteroatoms selected independently from O, S and N, wherein the cyclopentyl, cyclohexyl or
- 30 heterocyclic group may bear one or two substituents selected from oxo, hydroxy, halogeno,

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C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, carbamoyl, C_{1-4} alkylcarbamoyl, N,N -di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkanoyl and C_{1-4} alkoxycarbonyl;

- 7a) $-Y^1X^6R^{21}$ (wherein Y^1 , X^6 and R^{21} are as hereinabove defined); and
- 8a) $-Y^1-NR^{17}R^{18}$ (wherein Y^1 , R^{17} and R^{18} are as hereinabove defined).

5 More preferably R^4 is selected from one of the following groups:

1b) $-Y^1-R^{20}$;

2b) C_{1-3} alkoxy- Y^1 -;

3b) $-Y^1-X^6-R^{21}$;

4b) $-Y^1-NR^{17}R^{18}$;

10 wherein Y^1 , X^6 , R^8 , R^{17} , R^{18} , R^{20} and R^{21} are as hereinabove defined and Y^4 is a C_{2-5} alkylene chain wherein each methylene group (other than that of the α -carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno and amino, provided that there are no more than 3 substituents on the C_{2-5} alkylene chain;

Yet more preferably R^4 is selected from one of the following groups:

15 1c) $-Y^1-R^{22}$;

2c) C_{1-3} alkoxy- Y^1 -;

3c) $Y^1-X^6-R^{22}$;

4c) $-Y^1-NR^{17}R^{18}$;

wherein Y^1 , Y^4 , X^6 , R^8 , R^{17} and R^{18} are as hereinabove defined and R^{22} is cyclopentyl,

20 cyclohexyl, pyrrolidinyl, piperidinyl, azetidinyl, piperazinyl, homopiperidinyl, pyrrolyl, morpholino, thiomorpholino, morpholinyl, thiomorpholinyl, thiazolidinyl and 1,2,6-tetrahydropyridyl each of the aforementioned ring systems being optionally substituted by 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, C_{2-4} alkanoyl and C_{1-4} alkoxycarbonyl.

25 Preferably the alkylene, alkenylene or alkynylene group in Y^1 or Y^2 in R^4 is substituted by a hydroxy, halogeno, amino or C_{1-4} alkanoyloxy group on the β -carbon.

Preferably the alkylene, alkenylene or alkynylene group in Y^1 or Y^2 in R^4 is substituted by a hydroxy, halogeno or amino group on the β -carbon.

Preferably the alkylene, alkenylene or alkynylene chain in Y^1 or Y^2 in R^4 is substituted

30 by hydroxy or acetoxy.

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Preferably Y² in R⁴ is C_{2,5}alkylene wherein each methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno, amino and C_{1,4}alkanoyloxy provided that there is at least 1 substituent and no more than 3 substituents on the alkylene, alkenylene or alkynylene chain.

5 Preferably Y² in R⁴ is C_{2,5}alkylene wherein each methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno and amino, provided that there is at least 1 substituent and no more than 3 substituents on the alkylene, alkenylene or alkynylene chain.

Preferably Y¹ or Y² in R⁴ is substituted by only 1 substituent selected from hydroxy,
 10 halogeno, amino and acetoxy. More preferably Y¹ or Y² in R⁴ is an C_{2,5}alkylene chain which is substituted by 1 substituent, on the β-carbon, selected from hydroxy, halogeno, amino and acetoxy. Yet more preferably Y¹ or Y² in R⁴ is 2-hydroxypropylene, 2-acetoxypropylene or 2-hydroxybutylene. Especially preferably Y¹ or Y² in R⁴ is 2-hydroxypropylene or 2-acetoxypropylene.

15 Preferably Y¹ or Y² in R⁴ is substituted by only 1 substituent selected from hydroxy, halogeno and amino. More preferably Y¹ or Y² in R⁴ is an C_{2,5}alkylene chain which is substituted by 1 substituent, on the β-carbon, selected from hydroxy, halogeno and amino. Yet more preferably Y¹ or Y² in R⁴ is 2-hydroxypropylene or 2-hydroxybutylene. Most preferably Y¹ or Y² in R⁴ is 2-hydroxypropylene.

20 Preferably Y³ is C_{1,5}alkylene wherein each methylene group (other than that of the α-carbon) is optionally substituted by 1 substituent independently selected from hydroxy, halogeno and amino, provided that there are no more than 2 substituents on the alkylene, chain. More preferably Y³ in R⁴ is unsubstituted or substituted by 1 substituent selected from hydroxy, halogeno or amino. Yet more preferably Y³ in R⁴ is methylene, ethylene or
 25 propylene. Most preferably Y³ in R⁴ is methylene.

Preferably R⁴ is of the formula -Y²-R¹⁶, -Y²-NR¹⁷R¹⁸ or -Y³-R⁴, wherein Y², Y³, R⁴, R¹⁶, R¹⁷ and R¹⁸ are as hereinabove defined.

More preferably R⁴ is of the formula -Y¹-R¹⁶, -Y²-NR¹⁷R¹⁸ or -Y³-R⁴, wherein Y¹ and Y³ are as hereinabove defined, R¹⁶ is a 4 to 7-membered saturated or partially saturated

30 heterocyclic group containing one or two ring heteroatoms independently selected from O, S

and N and wherein the heterocyclic ring is optionally substituted as hereinabove defined, and R^o, R¹⁷ and R¹⁸ are as hereinabove defined.

Preferably R¹⁶ is a 4 to 7 membered saturated or partially saturated heterocyclic group containing one ring nitrogen atom and optionally containing one additional ring heteroatom selected from O, S and N and wherein the heterocyclic ring is linked to -Y²- through the ring nitrogen atom and wherein the heterocyclic ring is optionally substituted as hereinabove defined.

Preferred heterocyclic groups for R¹⁶ include pyrrolidine, piperidine, azetidine, piperazine, homopiperidine, pyrroline, morpholine, thiomorpholine, thiazolidine and 1,2,6-tetrahydropyridine.

Preferred optional substituents for a heterocyclic group in R¹⁶ include oxo, hydroxy, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₂₋₅cycloalkyl, or a 5- or 6-membered saturated or partially saturated heterocyclic ring containing one or two ring heteroatoms selected from O, S and N.

More preferred optional substituents for a heterocyclic group in R¹⁶ include, oxo, hydroxy, methyl, ethyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, methoxy, ethoxy, acetyl, cyclopropyl, vinyl, allyl and 2-morpholinoethyl.

Preferred optional substituents for ring carbon atoms in a heterocyclic group in R¹⁶ include methyl and hydroxy. Preferred optional substituents for ring nitrogen atoms in a heterocyclic group in R¹⁶ include C₁₋₄alkyl, hydroxyC₁₋₄alkyl, C₂₋₅alkenyl, C₂₋₅alkanoyl, C₂₋₅alkynyl, C₂₋₅cycloalkyl and C₁₋₃alkyl substituted by a heterocyclic group. More preferred optional substituents for ring nitrogen atoms in a heterocyclic group in R¹⁶ include methyl, 2-hydroxyethyl, allyl, 2-hydroxyethyl, 3-hydroxypropyl, cyclopropyl and 2-morpholinoethyl.

Preferably the heterocyclic group in R¹⁶ is unsubstituted.

Preferably R^o is C₃₋₇cycloalkyl wherein the ring is linked to -Y³- through a ring carbon atom which is substituted by hydroxy, amino or halogeno and wherein the ring is optionally further substituted as hereinabove defined.

More preferably R^o is C₃₋₇cycloalkyl wherein the ring is linked to -Y³- through a ring carbon atom which is substituted by hydroxy and wherein the ring is optionally substituted as hereinabove defined.

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Preferably R^a is hydroxycyclopropyl, hydroxycyclobutyl, hydroxycyclopentyl, hydroxycyclohexyl, wherein the hydroxy group is a substituent on the ring carbon atom linked to Y³ and the rings are optionally further substituted by 1 or 2 substituents selected from oxo, hydroxy, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₂₋₅cycloalkyl, or a 5 5- or 6-membered saturated or partially saturated heterocyclic ring containing one or two ring heteroatoms selected from O, S and N.

Most preferably R^a is 1-hydroxycyclopentyl or 1-hydroxycyclohexyl.

Preferred substituents for R^a are as hereinabove defined for R¹⁶.

Preferably R¹⁷ and R¹⁸ in NR¹⁷R¹⁸ are independently selected from hydrogen, C₁₋₁₀alkyl, hydroxyC₁₋₄alkyl, cyanoC₁₋₄alkyl, C₂₋₅alkenyl, C₂₋₅alkynyl, C₁₋₄alkoxylC₁₋₃alkyl, and hydroxyC₁₋₃alkoxyC₁₋₃alkyl.

More preferably R¹⁷ and R¹⁸ in NR¹⁷R¹⁸ are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, 2-methylpropyl, cyanomethyl, 2-cyanoethyl, 2-hydroxyethyl, vinyl, allyl, 2-(ethoxy)ethyl and 2-(2-hydroxyethoxy)ethyl. Preferably one of 15 R¹⁷ and R¹⁸ is hydrogen or methyl.

Most preferably R¹⁷ and R¹⁸ are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, 2-methylpropyl, and allyl.

A particular class of compounds is of the formula (I) wherein:

ring A is phenyl or pyridyl, especially phenyl;

20 m is 1, 2 or 3;

Z, R¹, R² and R³ are as hereinbefore defined; X¹ is -O-, -S-, -NR⁷CO-, -NR⁷SO₂- or -NR⁷- (wherein R⁷ is hydrogen, methyl, ethyl, methoxyethyl or ethoxyethyl); and R⁴ is selected from groups 1a) to 8a) as hereinabove defined;

provided that when:

25 m is an integer from 1 to 3;

R¹ is methoxy; R² is hydrogen; Z is -NH-;

R³ is halogeno or C₁₋₃alkyl; and

X¹ is -O-; then

R⁴ is not selected from one of the following three groups:

30 a) -C₂₋₅alkylR¹⁹ (wherein R¹⁹ is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

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- b) $-C_{2,5}\text{alkenyl}R^{19}$ (wherein R^{19} is as defined hereinbefore);
- c) $-C_{2,5}\text{alkynyl}R^{19}$ (wherein R^{19} is as defined hereinbefore);
wherein any alkyl, alkenyl or alkynyl group is optionally substituted by one or more substituents selected from hydroxy, halogeno and amino;
- 5 or a pharmaceutically-acceptable salt or prodrug thereof.

A further particular class of compound is of the formula (I) wherein:

- ring A is phenyl;
- m is 1, 2 or 3; Z is $-\text{NH}-$;
- R^1, R^2 and R^3 are as hereinabove defined; X^1 is $-\text{O}-$, $-\text{S}-$, $-\text{NR}^7\text{CO}-$, $-\text{NR}^7\text{SO}_2-$ or $-\text{NR}^7-$
- 10 (wherein R^7 is hydrogen, methyl, ethyl or methoxyethyl); and R^4 is selected from groups 1b) to 4b) as hereinabove defined;
provided that when:
- m is an integer from 1 to 3;
- R^1 is methoxy; R^2 is hydrogen; Z is $-\text{NH}-$;
- 15 R³ is halogeno or $C_{1,3}\text{alkyl}$; and
 X^1 is $-\text{O}-$; then
R⁴ is not selected from one of the following three groups:
 - a) $-C_{2,5}\text{alkyl}R^{19}$ (wherein R^{19} is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, $C_{1,4}\text{alkyl}$, $C_{1,4}\text{hydroxalkyl}$ and $C_{1,4}\text{alkoxy}$);
 - 20 b) $-C_{2,5}\text{alkenyl}R^{19}$ (wherein R^{19} is as defined hereinbefore);
 - c) $-C_{2,5}\text{alkynyl}R^{19}$ (wherein R^{19} is as defined hereinbefore);
wherein any alkyl, alkenyl or alkynyl group is optionally substituted by one or more substituents selected from hydroxy, halogeno and amino;
or a pharmaceutically-acceptable salt or prodrug thereof.
- 25 A further particular class of compounds of the formula (I) wherein:
ring A is phenyl;
m is 1, 2 or 3;
Z is $-\text{NH}-$;
 R^1, R^2 and R^3 are as hereinabove defined; X^1 is $-\text{O}-$, $-\text{S}-$, $-\text{NR}^7\text{CO}-$, $-\text{NR}^7\text{SO}_2-$ or
30 $-\text{NR}^7-$ (wherein R^7 is hydrogen, methyl, ethyl or methoxyethyl); and R^4 is selected from groups 1c) to 4c) as hereinabove defined;

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provided that when:

m is an integer from 1 to 3;

R^1 is methoxy; R^2 is hydrogen; Z is $-NH-$;

R^3 is halogeno or C_{1-3} alkyl; and

5 X^1 is $-O-$; then

R^4 is not selected from one of the following three groups:

a) $-C_{2-5}alkylR^{19}$ (wherein R^{19} is piperidin-4-yl which may bear one or two substituents

selected from hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} alkoxy);

b) $-C_{2-5}alkenylR^{19}$ (wherein R^{19} is as defined hereinbefore);

10 c) $-C_{2-5}alkynylR^{19}$ (wherein R^{19} is as defined hereinbefore);

wherein any alkyl, alkenyl or alkynyl group is optionally substituted by one or more substituents selected from hydroxy, halogeno and amino;

or a pharmaceutically-acceptable salt or prodrug thereof.

Yet a further particular class of compounds is of the formula (I) wherein:

15 ring A is phenyl;

m is 1, 2 or 3;

Z is $-NH-$;

R^1 , R^2 and R^3 are as hereinabove defined;

X^1 is $-O-$ or $-S-$; and

20 R^4 is of the formula $-Y^1R^{20}$ or $Y^1NR^{17}R^{18}$ as hereinabove defined;

provided that when:

m is an integer from 1 to 3;

R^1 is methoxy; R^2 is hydrogen; Z is $-NH-$;

R^3 is halogeno or C_{1-3} alkyl; and

25 X^1 is $-O-$; then

R^4 is not selected from one of the following three groups:

a) $-C_{2-5}alkylR^{19}$ (wherein R^{19} is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl and C_{1-4} alkoxy);

b) $-C_{2-5}alkenylR^{19}$ (wherein R^{19} is as defined hereinbefore);

30 c) $-C_{2-5}alkynylR^{19}$ (wherein R^{19} is as defined hereinbefore);

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or a pharmaceutically-acceptable salt or prodrug thereof.

Yet a further particular class of compounds if of the formula (I) wherein:

ring A is phenyl;

Z is -NH-;

5 m is 1, 2 or 3;

R¹ is hydrogen or methoxy;

R² is hydrogen;

R³ is fluoro, chloro, bromo, methyl or methoxy;

X¹ is -O- or -S-; and

10 R⁴ is of the formula -Y¹-R²⁰ or -Y¹-NR¹⁷R¹⁸ (wherein Y¹, R¹⁷, R¹⁸ and R²⁰ are as hereinabove defined;

provided that when:

m is an integer from 1 to 3;

R¹ is methoxy; R² is hydrogen; Z is -NH-;

15 R³ is halogeno or C₁₋₃alkyl; and

X¹ is -O-; then

R⁴ is not selected from one of the following three groups:

a) -C₂₋₅alkylR¹⁹ (wherein R¹⁹ is piperidin-4-yl which may bear one or two substituents selected from hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy);

20 b) -C₂₋₅alkenylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

c) -C₂₋₅alkynylR¹⁹ (wherein R¹⁹ is as defined hereinbefore);

wherein any alkyl, alkenyl or alkynyl group is optionally substituted by one or more substituents selected from hydroxy, halogeno and amino;

or a pharmaceutically-acceptable salt or prodrug thereof.

25 Particular compounds of the present invention include:

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxy)quinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxy)quinazoline

30 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxy)quinazoline

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4-(4-chloro-2-fluorophenylamino)-7-(2-hydroxy-3-(morpholino)propoxy)-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(thiazolidin-3-yl)propoxy]-6-methoxyquinazoline

5 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(3-pyrrolin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-(2-morpholinoethyl)piperazin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-(3-hydroxypropyl)piperazin-1-yl)propoxy]-6-methoxyquinazoline

10 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy]-6-methoxyquinazoline

15 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-tertbutyl-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline hydrochloride

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isobutyl-N-methylamino)propoxy]-6-methoxyquinazoline

20 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(morpholino)propoxy]-6-methoxyquinazoline

25 4-(4-bromo-2-fluorophenylamino)-7-(2-hydroxy-3-(N,N-dimethylamino)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(piperidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

30 methoxyquinazoline

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4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(piperidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(homopiperidin-1-yl)propoxy]-6-methoxyquinazoline

5 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(thiazolidin-3-yl) propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(3-pyrrolin-1-yl)propoxy]-6-methoxyquinazoline

10 10 methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(thiomorpholin-4-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(3-hydroxypyrrrolidin-1-yl)propoxy]-6-methoxyquinazoline

15 15 4-(4-chloro-2-fluorophenylamino)-7-{2-hydroxy-3-[4-(2-morpholinoethyl)piperazin-1-yl]propoxy}-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-{2-hydroxy-3-[4-(3-hydroxypropyl)piperazin-1-yl]propoxy}-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-{2-hydroxy-3-[4-(2-hydroxyethyl)]piperazin-1-yl}propoxy}-6-methoxyquinazoline

20 20 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(azetidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy]-6-methoxyquinazoline

25 25 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(4-methylpiperidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(prop-2-yn-1-yl)-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(2-methylpyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

30 30 methoxyquinazoline

-29-

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(2-cyanoethyl)-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline

5 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isobutyl-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(n-propyl)-N-ethylamino)propoxy]-6-methoxyquinazoline; and

pharmaceutically-acceptable salts thereof; and additional particular compounds of the present
10 invention are

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-pyridylsulphonyl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(1-methylimidazol-2-ylsulphonyl)propoxy]-6-methoxyquinazoline

15 4-chloro-2-fluoro-5-hydroxyphenylamino-7-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

4-chloro-2-fluoro-5-hydroxyphenylamino-7-(2-acetoxy-3-piperidinopropoxy)-6-methoxyquinazoline

4-bromo-2-fluoro-5-hydroxyphenylamino-7-[2-acetoxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxyquinazoline
20 and

pharmaceutically-acceptable salts thereof.

Preferred compounds of the present invention are

25 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinazoline
30 and

-30-

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(thiazolidin-3-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(3-pyrrolin-1-yl)propoxy]-6-methoxyquinazoline

5 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-(2-morpholinoethyl)piperazin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-(3-hydroxypropyl)piperazin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(4-(2-hydroxyethyl)piperazin-1-yl)propoxy]-6-methoxyquinazoline

10 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-tertbutyl-N-methylamino)propoxy]-6-methoxyquinazoline

15 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline hydrochloride

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isobutyl-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(2-hydroxyethyl)-N-

20 methylamino)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(morpholino)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(N,N-dimethylamino)propoxy]-6-methoxyquinazoline

25 4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(piperidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-bromo-2-fluorophenylamino)-7-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N,N-dimethylamino)propoxy]-6-

30 methoxyquinazoline

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4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(homopiperidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-6-methoxyquinazoline

5 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(3-pyrrolin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(thiomorpholin-4-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(3-hydroxypyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

10 4-(4-chloro-2-fluorophenylamino)-7-{2-hydroxy-3-[4-(2-morpholinoethyl)piperazin-1-yl]propoxy}-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-{2-hydroxy-3-[4-(2-hydroxyethyl)]piperazin-1-yl}propoxy}-6-methoxyquinazoline

15 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(2,5-dimethyl-3-pyrrolin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(4-methylpiperidin-1-yl)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(2-methylpyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

20 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-(2-cyanoethyl)-N-methylamino)propoxy]-6-methoxyquinazoline

4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxyquinazoline

25 4-(4-chloro-2-fluorophenylamino)-7-[2-hydroxy-3-(N-isobutyl-N-methylamino)propoxy]-6-methoxyquinazoline

4-chloro-2-fluoro-5-hydroxyphenylamino-7-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxyquinazoline

4-chloro-2-fluoro-5-hydroxyphenylamino-7-(2-acetoxy-3-piperidinopropoxy)-6-methoxyquinazoline

30 methoxyquinazoline

4-bromo-2-fluoro-5-hydroxyphenylamino-7-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy]-6-methoxyquinazoline; and
pharmaceutically-acceptable salts thereof.

The present invention relates to the compounds of formula I as hereinbefore defined

5 as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such

10 salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts

15 may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

20 Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H.

25 Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

30 An example of a prodrug is an *in vivo* hydrolysable ester formed at a hydroxy group. An *in vivo* hydrolysable ester of a compound of the formula I containing a hydroxy

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or animal body to produce the parent alcohol. The term includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A
 5 selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxy carbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

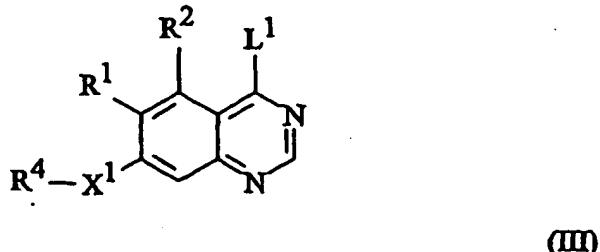
A compound of the formula I, or salt thereof, and other compounds of the invention
 10 (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications, Publication Nos. 0520722, 0566226, 0602851, 0635498, 0873319, 0880508 and 0929530. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be
 15 obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus the following processes (a) to (f) and (i) to (vi) constitute further features of the
 20 present invention.

Synthesis of Compounds of Formula I

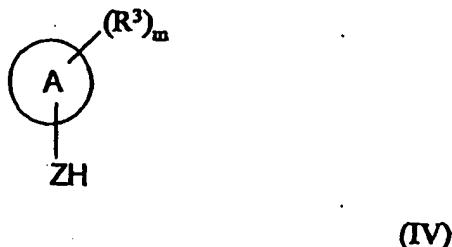
(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula III:

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(wherein R¹, R², X¹ and R⁴ are as defined hereinbefore and L¹ is a displaceable moiety), with a compound of the formula IV:



5

(wherein ring A, Z, R³ and m are as defined hereinbefore) whereby to obtain compounds of the formula I and salts thereof. A convenient displaceable moiety L¹ is, for example, a halogeno, alkoxy (preferably C₁₋₄alkoxy), aryloxy, alkylsulphanyl, arylsulphanyl, alkoxyalkylsulphanyl or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methylsulphanyl, 2-methoxyethylsulphanyl, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is advantageously effected in the presence of either an acid or a base. Such an acid is, for example, an anhydrous inorganic acid such as hydrogen chloride. Such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, tetramethylguanidine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, or an alkali metal or alkaline earth metal amide, for example sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. Preferably, when ring a is heterocyclic a

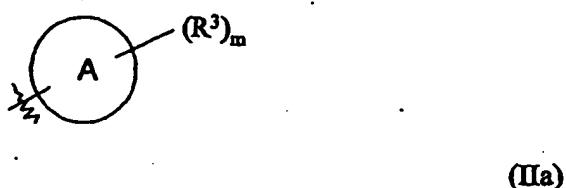
-35-

base is used. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 80°C.

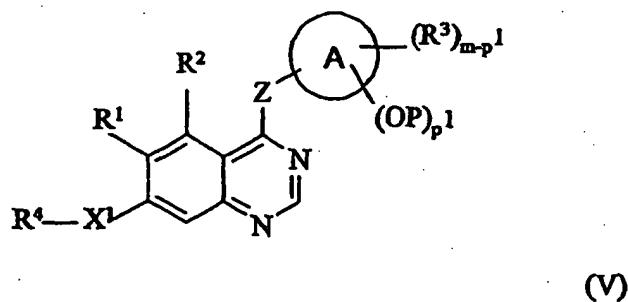
The compound of the invention may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula 5 H-L¹ wherein L¹ has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a base as defined hereinbefore using a conventional procedure.

(b) Where the group of formula IIa:

10



(wherein ring A, R³ and m are as hereinbefore defined) is a ring carrying one or more hydroxy groups, a compound of the formula I and salts thereof can be prepared by the 15 deprotection of a compound of formula V:

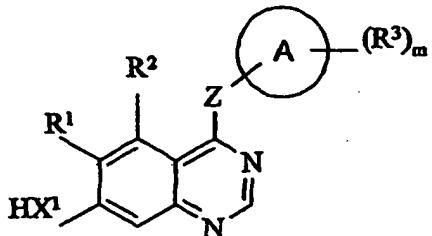


20 (wherein ring A, X¹, m, R¹, R², R³, R⁴ and Z are as hereinbefore defined, P is a hydroxy protecting group and p¹ is an integer from 1 to 5 equal to the number of protected hydroxy groups and such that m-p¹ is equal to the number of R³ substituents which are not protected hydroxy). The choice of hydroxy protecting group P is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in 25 Organic Synthesis" T.W. Greene and R.G.M. Wuts, 2nd Ed. Wiley 1991, including ethers (for example, methyl, methoxymethyl, allyl and benzyl), silyl ethers (for example,

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t-butyldiphenylsilyl and t-butyldimethylsilyl), esters (for example, acetate and benzoate) and carbonates (for example, methyl and benzyl). The removal of such a hydroxy protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in standard texts such as that indicated hereinbefore, or by 5 a related procedure. The reaction conditions preferably being such that the hydroxy derivative is produced without unwanted reactions at other sites within the starting or product compounds. For example, where the protecting group P is acetate, the transformation may conveniently be effected by treatment of the quinazoline derivative with a base as defined hereinbefore and including ammonia, and its mono and di-alkylated derivatives, preferably in 10 the presence of a protic solvent or co-solvent such as water or an alcohol, for example methanol or ethanol. Such a reaction can be effected in the presence of an additional inert solvent or diluent as defined hereinbefore and at a temperature in the range 0 to 50°C, conveniently at about 20°C.

(c) Production of those compounds of formula I and salts thereof wherein the 15 substituent X¹ is -O-, -S- or -NR⁷- can be achieved by the reaction, conveniently in the presence of a base as defined hereinbefore, of a compound of the formula VI:



(VI)

20

(wherein ring A, m, X¹, R¹, R², R³, and Z are as hereinbefore defined) with a compound of formula VII:



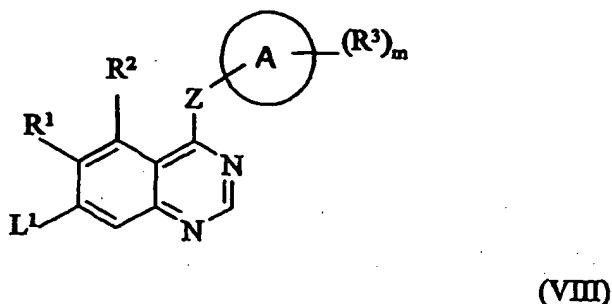
(VII)

25

(wherein R⁴ and L¹ are as hereinbefore defined); L¹ is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo or methanesulphonyloxy group. The

reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 50°C.

5 (d) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula VIII:



10

with a compound of the formula IX:

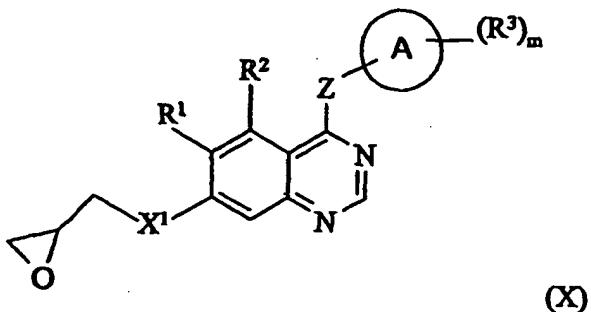


15 (wherein ring A, L¹, R¹, R², R³, R⁴, Z, m and X¹ are all as hereinbefore defined). The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

20 e) Compounds of the formula (I) and salts thereof wherein R⁴ is a 2-hydroxypropyl chain substituted by -NR¹⁷R¹⁸ (wherein R¹⁷ and R¹⁸ are as hereinabove defined) or a saturated or partially saturated heterocyclic ring containing and linked through a ring nitrogen atom and containing up to 2 additional ring heteroatoms selected from O, S and N, by reacting a compound of the formula X:

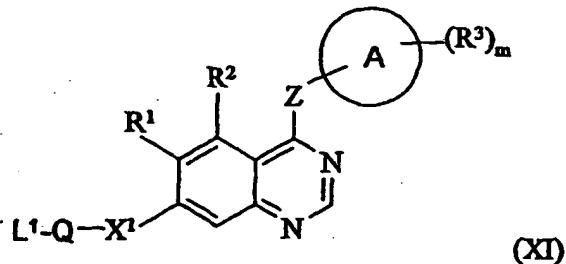
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(wherein ring A, R¹, R², R³, Z, m and X¹ are all as hereinbefore defined) with the appropriate amine. The reaction is conveniently carried out in an inert organic solvent such as ethanol or 5 chloroform in a temperature range of 0°C to 100°C. Analogous reactions may be used to produce compounds of the formula (1) wherein R⁴ comprises longer hydroxy-substituted alkylene, alkenylene or alkynylene chains.

f) Compounds of the formula (I) and salts thereof wherein the group in R⁴ linked to -Y¹- or -Y²- is linked via a N, O or S atom may be prepared by reacting a compound of the 10 formula (XI):

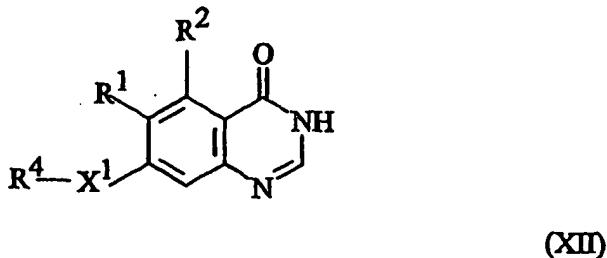


(wherein ring A, L¹, X¹, R¹, R², R³, Z and m are as hereinabove defined and Q is -Y¹- or -Y²- 15) with the appropriate compound containing a HN, HO or HS group. The reaction is conveniently carried out in the presence of a base (as hereinabove defined in process (a)) in the presence of an inert organic solvent (as defined in process (a)), in a temperature range of 0°C to 150°C.

Synthesis of Intermediates

(i) The compounds of formula III and salts thereof, constitute a further feature of the present invention. Such compounds in which L¹ is halogeno may for example be prepared by halogenating a compound of the formula XII:

5



(wherein R¹, R², R⁴ and X¹ are as hereinbefore defined).

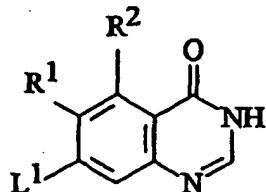
Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxychloride and phosphorus(V)chloride.

The halogenation reaction is conveniently effected in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene. The reaction is conveniently effected at a temperature in the range, for example

15 10 to 150°C, preferably in the range 40 to 100°C.

The compounds of formula XII and salts thereof which constitute a further feature of the present invention may for example be prepared by reacting a compound of the formula XIII:

20



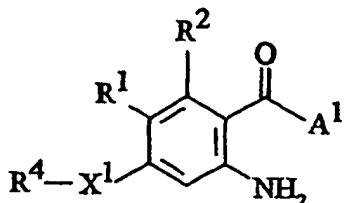
(wherein R¹, R² and L¹ are as hereinbefore defined) with a compound of the formula IX as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or

-40-

diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

The compounds of formula XII and salts thereof may also be prepared by cyclising a compound of the formula XIV:

5

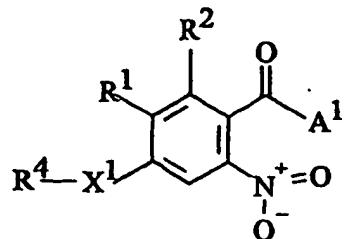


(XIV)

(wherein R¹, R², R⁴ and X¹, are as hereinbefore defined, and A¹ is an hydroxy, alkoxy (preferably C₁-4alkoxy) or amino group) whereby to form a compound of formula XII or salt thereof. The cyclisation may be effected by reacting a compound of the formula XIV, where A¹ is an hydroxy or alkoxy group, with formamide or an equivalent thereof effective to cause cyclisation whereby a compound of formula XII or salt thereof is obtained, such as [3-(dimethylamino)-2-azaprop-2-enylidene]dimethylammonium chloride. The cyclisation is conveniently effected in the presence of formamide as solvent or in the presence of an inert solvent or diluent such as an ether for example 1,4-dioxan. The cyclisation is conveniently effected at an elevated temperature, preferably in the range 80 to 200°C. The compounds of formula XII may also be prepared by cyclising a compound of the formula XIV, where A¹ is an amino group, with formic acid or an equivalent thereof effective to cause cyclisation whereby a compound of formula XII or salt thereof is obtained. Equivalents of formic acid effective to cause cyclisation include for example a tri-C₁-4alkoxymethane, for example triethoxymethane and trimethoxymethane. The cyclisation is conveniently effected in the presence of a catalytic amount of an anhydrous acid, such as a sulphonic acid for example p-toluenesulphonic acid, and in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as diethylether or tetrahydrofuran, or an aromatic hydrocarbon solvent such as toluene. The cyclisation is conveniently effected at a temperature in the range, for example 10 to 100°C, preferably in the range 20 to 50°C.

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Compounds of formula XIV and salts thereof, which constitute a further feature of the present invention, may for example be prepared by the reduction of the nitro group in a compound of the formula XV:



5

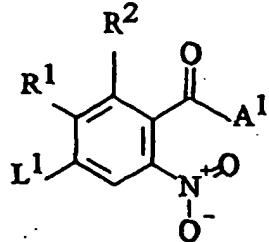
(XV)

(wherein R¹, R², R⁴, X¹ and A¹ are as hereinbefore defined) to yield a compound of formula XIV as hereinbefore defined. The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out,

- 10 for example, by the hydrogenation of a solution of the nitro compound in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal effective to catalyse hydrogenation reactions such as palladium or platinum. A further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the
- 15 reduction may be effected by heating the nitro compound and the activated metal in the presence of a solvent or diluent such as a mixture of water and alcohol, for example methanol or ethanol, to a temperature in the range, for example 50 to 150°C, conveniently at about 70°C.

Compounds of the formula XV and salts thereof which constitute a further feature of the

- 20 present invention, may for example be prepared by the reaction of a compound of the formula XVI:

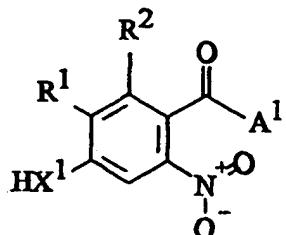


(XVI)

(wherein R¹, R², L¹ and A¹ are as hereinbefore defined) with a compound of the formula IX as hereinbefore defined to give a compound of the formula XV. The reaction of the compounds of formulae XVI and IX is conveniently effected under conditions as described for process

5 (d) hereinbefore.

Compounds of formula XV and salts thereof, may for example also be prepared by the reaction of a compound of the formula XVII:

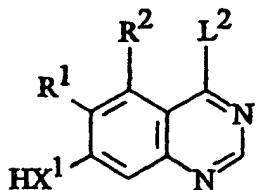


(XVII)

10

(wherein R¹, R², X¹ and A¹ are as hereinbefore defined with the proviso that X¹ is not -CH₂-) with a compound of the formula VII as hereinbefore defined to yield a compound of formula XV as hereinbefore defined. The reaction of the compounds of formulae XVII and VII is conveniently effected under conditions as described for process (c) hereinbefore.

15 The compounds of formula III and salts thereof may also be prepared for example by reacting a compound of the formula XVIII:



(XVIII)

20 (wherein R¹, R² and X¹ are as hereinbefore defined with the proviso that X¹ is not -CH₂- and L² is a displaceable protecting moiety) with a compound of the formula VII as hereinbefore defined, whereby to obtain a compound of formula III in which L¹ is represented by L².

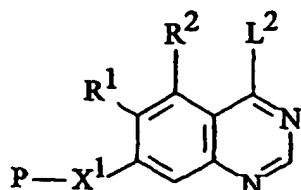
A compound of formula XVIII is conveniently used in which L² is a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2 substituents, selected from

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halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (c) hereinbefore.

The compounds of formula XVIII and salts thereof as hereinbefore defined may for example be prepared by deprotecting a compound of the formula XIX:

5

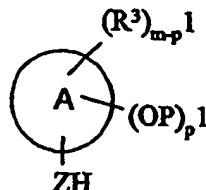


(XIX)

(wherein R¹, R², P, X¹ and L² are as hereinbefore defined with the proviso that X¹ is not -CH₂-). Deprotection may be effected by techniques well known in the literature, for example

10 where P is a benzyl group deprotection may be effected by hydrogenolysis or by treatment with trifluoroacetic acid.

One compound of formula III may if desired be converted into another compound of formula III in which the moiety L¹ is different. Thus for example a compound of formula III in which L¹ is other than halogeno, for example optionally substituted phenoxy, may be
 15 converted to a compound of formula III in which L¹ is halogeno by hydrolysis of a compound of formula III (in which L¹ is other than halogeno) to yield a compound of formula XII as hereinbefore defined, followed by introduction of halide to the compound of formula XII, thus obtained as hereinbefore defined, to yield a compound of formula III in which L¹ is halogen.
 20 (ii) The compounds of formula V and salts thereof, constitute a further feature of the present invention, and may for example be prepared by the reaction of a compound of formula III as hereinbefore defined with a compound of the formula XX:

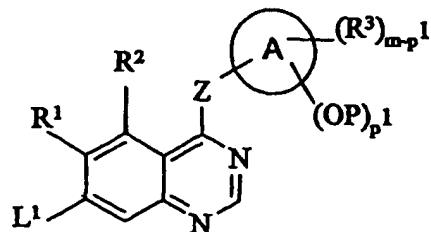


(XX)

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(wherein ring A, R³, m, p¹, P and Z are as hereinbefore defined). The reaction may for example be effected as described for process (a) hereinbefore.

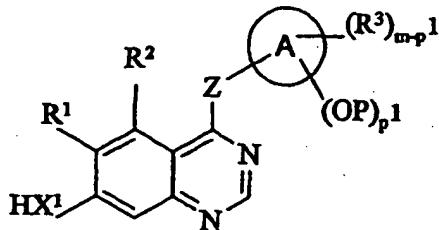
The compounds of formula V and salts thereof may also be prepared by reacting a 5 compound of formula XXI:



(XXI)

(wherein ring A, R¹, R², L¹, Z, R³, m, p¹ and P are as hereinbefore defined) with a compound 10 of formula IX as hereinbefore defined. The reaction may for example be effected as described for process (d) above.

The compounds of formula V and salts thereof may also be prepared by reacting a compound of formula XXII:



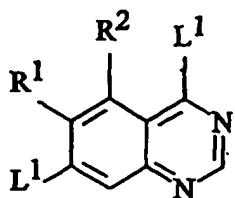
15

(XXII)

(wherein ring A, R¹, R², R³, X¹, Z, P, p¹ and m are as hereinbefore defined with the proviso that X¹ is not -CH₂-) with a compound of the formula VII as hereinbefore defined. The 20 reaction may for example be effected as described for process (c) hereinbefore.

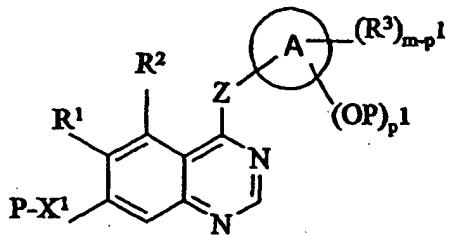
The compounds of formula XXI and salts thereof may for example be prepared by reaction of a compound of formula XXIII:

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(wherein R¹, R², and L¹ are as hereinbefore defined, and L¹ in the 4- and 7- positions may be
5 the same or different) with a compound of the formula XX as hereinbefore defined. The reaction may be effected for example by a process as described in (a) above.

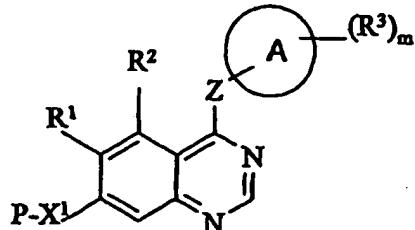
Compounds of the formula XXII and salts thereof may be made by reacting compounds of the formulae XIX and XX as hereinbefore defined, under conditions described in (a) hereinbefore, to give a compound of formula XXIV:



(XXIV)

(wherein ring A, R¹, R², R³, P, Z, X¹, p¹ and m are as hereinbefore defined with the proviso that X¹ is not -CH₂-) and then deprotecting the compound of formula XXIV for example as described in (i) above.

15 (iii) Compounds of the formula VI as hereinbefore defined and salts thereof may be made by deprotecting the compound of formula XXV:



(XXV)

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(wherein ring A, R¹, R², R³, P, Z, X¹ and m are as hereinbefore defined) by a process for example as described in (i) above.

Compounds of the formula XXV and salts thereof may be made by reacting compounds of the formulae XIX and IV as hereinbefore defined, under the conditions

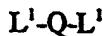
5 described in (a) hereinbefore, to give a compound of the formula XXV or salt thereof.

(iv) Compounds of the formula VIII and salts thereof as hereinbefore defined may be made by reacting compounds of the formulae XXIII and IV as hereinbefore defined, the reaction for example being effected by a process as described in (a) above.

(v) Compounds of the formula (X) can be prepared by reacting the appropriate epoxy

10 compound substituted with a leaving group such as halo (for example in the case of Y¹ or Y² being 2,3-epoxyprop-1-yl, 1-bromo-2,3-epoxyp propane may be used) with a compound of the formula (XXV) (for example the 7-hydroxyquinazoline derivative). The reaction is conveniently carried out in the presence of a mild base such as metal carbonate (e.g potassium carbonate).

15 (vi) Compounds of the formula XI as defined hereinbefore and salts thereof may for example be made by the reaction of a compound of formula VI as defined hereinbefore with a compound of the formula XXVI:



20

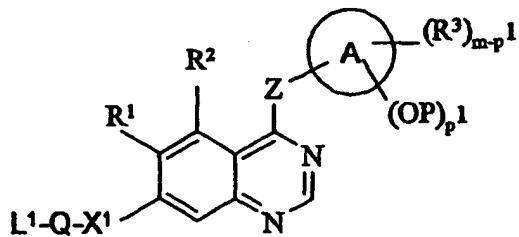
(XXVI)

(wherein L¹ and Q are as hereinbefore defined) to give a compound of the formula XI. The reaction may be effected for example by a process as described in (c) above.

Compounds of the formula XI and salts thereof may also be made for example by

25 deprotecting a compound of the formula XXVII:

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5 (wherein ring A, L¹, Q, X¹, R¹, R², R³, Z, P, m and p¹ are as defined hereinbefore) by a process for example as described in (b) above.

Compounds of the formula XXVII and salts thereof may be made for example by reacting compounds of the formulae XXII and XXVI as defined hereinbefore, under the conditions described in (c) above.

10 When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure, the acid having a pharmaceutically acceptable anion.

Some of the intermediates defined herein are novel, for example, those of the formulae V and X and these are provided as a further feature of the invention.

15 Optional substituents may be converted into other optional substituents. For example an alkylthio group may be oxidised to an alkylsulphanyl or alkysulphonyl group, a nitro group reduced to an amino group, a hydroxy group alkylated to a methoxy group, or a bromo group converted to an alkylthio group.

Various substituents may be introduced into compounds of the formulae (I) and
20 intermediates in the preparation of the formulae (I) and intermediates in the preparation of compounds of the formulae (I), when appropriate, using standard methods known in the art. For example, a nitro group may be introduced into an activated benzene ring by nitration with concentrated nitric acid concentrated sulphuric acid and bromination with bromine or tetra (n-butyl) ammonium tribromide.

25 It will be appreciated that, in certain steps in the reaction sequence to compounds of the formula (I), it will be necessary to protect certain functional groups in intermediates in order to prevent side reactions. Deprotection may be carried out at a convenient stage in the reaction sequence once protection is no longer required.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled 5 chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is 10 applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive.

Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

15 A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy-lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower 20 acyloxy-lower alkyl groups, (for example acetoxyethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and 25 tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups 30 (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower

alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

5 Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxycarbonyl,

10 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as

15 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to 'Advanced Organic Chemistry', 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to 'Protective Groups in Organic Synthesis', 2nd Edition, by T. Greene and

20 R.G.M. Wuts, for general guidance on protecting groups.

The identification of compounds which potently inhibit the tyrosine kinase activity associated with VEGF receptors such as Flt and/or KDR and which inhibit angiogenesis and/or increased vascular permeability is desirable and is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out

25 below:

(a) In Vitro Receptor Tyrosine Kinase Inhibition Test

This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF, FGF or EGF receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by

30 cloning. These may then be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example VEGF, FGF and EGF receptor cytoplasmic

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domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon,

5 described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant construct was co-transfected into insect cells (for example Spodoptera frugiperda

10 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory

15 Manual, W. H. Freeman and Co, New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947), methionine 668 (EGF receptor, Genbank accession number X00588) and methionine 399 (FGF R1 receptor, Genbank accession number X51803) may be cloned and expressed in a similar manner.

20 For expression of cFlt tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol bis(β-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was

25 removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM sodium orthovanadate,

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0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock enzyme is diluted 1 in 2000 with enzyme diluent and 50µl of dilute enzyme is used for each assay well.

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in 5 PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells 10 were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25µl of diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM 15 manganese(II)chloride containing 8µM adenosine-5'-triphosphate (ATP) was added to all test wells except "blank" control wells which contained manganese(II)chloride without ATP. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine 20 antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST 25 containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 30 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at

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room temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

5

(b) *In Vitro* HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3 μ g/ml heparin + 1 μ g/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% CO₂. On day 4 the cultures were pulsed with 1 μ Ci/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

20 **(c) *In Vivo* Solid Tumour Disease Model**

This test measures the capacity of compounds to inhibit solid tumour growth.

CaLu-6 tumour xenografts were established in the flank of female athymic Swiss *nu/nu* mice, by subcutaneous injection of 1x10⁶ CaLu-6 cells/mouse in 100 μ l of a 50% (v/v) solution of Matrigel in serum free culture medium. Ten days after cellular implant, mice 25 were allocated to groups of 8-10, so as to achieve comparable group mean volumes.

Tumours were measured using vernier calipers and volumes were calculated as: $(l \times w) \times \sqrt{(l \times w)} \times (\pi/6)$, where l is the longest diameter and w the diameter perpendicular to the longest. Test compounds were administered orally once daily for a minimum of 21 days, and control animals received compound diluent. Tumours were measured twice weekly. The level of 30 growth inhibition was calculated by comparison of the mean tumour volume of the control

group versus the treatment group using a Student T test and/or a Mann-Whitney Rank Sum Test. The inhibitory effect of compound treatment was considered significant when $p<0.05$.

Although the pharmacological properties of the compounds of Formula I vary with structural change, in general, activity possessed by compounds of the Formula I, may be 5 demonstrated at the following concentrations or doses in one or more of the above tests (a) and (b):

Test (a):- IC_{50} in the range, for example, $< 10\mu M$;

Test (b):- IC_{50} in the range, for example, $< 10\mu M$;

For example in test (a), Example 1 had an IC_{50} of $0.015 - 0.05\mu M$ using the KDR 10 receptor.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

15 The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional 20 manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately $0.1-100\text{mg/kg}$. A unit dose in the range, for example, $1-100\text{mg/kg}$, preferably 25 $1-50\text{mg/kg}$ is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example $1-250\text{mg}$ of active ingredient.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use 30 in a method of treatment of the human or animal body by therapy.

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We have found that compounds of the present invention inhibit VEGF receptor tyrosine kinase activity and are therefore of interest for their antiangiogenic effects and/or their ability to cause a reduction in vascular permeability.

A further feature of the present invention is a compound of formula I, or a

5 pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a

10 compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded

15 animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated,

20 the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

25 The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice

30 to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the

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antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

- (i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxine, thalidomide), and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate));
- 5 (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and
- 10 (iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotapec); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide,
- 15 20 amsacrine, topotecan, and also irinotecan); also enzymes (for example asparaginase); and thymidylate synthase inhibitors (for example raltitrexed);

and additional types of chemotherapeutic agent include:

- (iv) biological response modifiers (for example interferon); and
- (v) antibodies (for example edrecolomab).

For example such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of a compound of formula I as defined hereinbefore, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchinol-O-phosphate (Example 1 of WO 99/02166).

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of VEGF receptor tyrosine kinase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated :-

30 (i) operations were carried out at ambient temperature; i.e. in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

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(ii) evaporation were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck 5 Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields, where present, are given for illustration only and are not necessarily the maximum attainable;

10 (v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic 15 resonance spectra were determined using a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by 20 thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

25 and

(viii) the following abbreviations have been used:-

DMF	<u>N,N</u> -dimethylformamide
DMSO	dimethylsulphoxide
TFA	trifluoroacetic acid